

Scientific Abstract

Heart failure secondary to systolic dysfunction is a disease of epidemic proportions in the U.S. Despite recent advances in therapy, the 5-year survival for severely affected individuals remains below 50%. Ventricular assist devices (VADs) provide a bridge between end-stage heart failure and cardiac transplantation. Unfortunately, insufficient donor hearts are available and only a small subset of patients improves sufficiently to be weaned from VAD support.

The sarcoplasmic reticulum calcium ATPase 2a (SERCA2a), which pumps calcium from the cytoplasm into the sarcoplasmic reticulum, is downregulated in heart failure. Restoring SERCA2a levels using adenoviral or adeno-associated viral vectors improves function, metabolism and survival in animal models of heart failure and in failing human myocytes. We therefore propose a Phase I trial at two sites (University of Pittsburgh, Massachusetts General Hospital) to test the hypothesis that expression of SERCA2a in the hearts of patients on VAD support will be safe, and to document whether SERCA2a overexpression improves cardiac function and the ability of patients to wean from VAD support.

We will randomize patients with a non-ischemic cardiomyopathy to direct injection of an adeno-associated viral vector expressing SERCA2a driven by the promiscuous CMV promoter (AAV6-CMV-SERCA2a; n=8) or saline (n=8) at the time of VAD insertion. During the period of VAD support, we will determine adverse events and search for improvement in ventricular function during weaning trials using echocardiography and metabolic stress testing. At the time of VAD explant, tissue studies will be performed to identify the extent of SERCA2a expression and evidence of inflammation. In addition, molecular markers of heart failure severity and isolated cell function will be compared for subjects and controls in injected areas and non-injected areas. If successful, this study will be the first human trial of gene therapy using AAV for patients with heart failure, and will provide the basis for a novel potential therapy for this devastating illness.